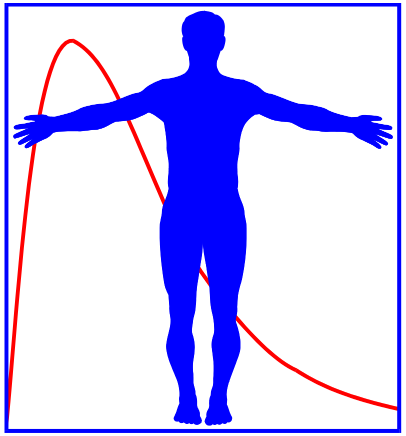
Population Modelling by Examples II

by the Population Modelling Working Group



Robert Smith?

Department of Mathematics and Faculty of Medicine
The University of Ottawa

Introduction

- Population modelling spans many domains and techniques
- New technologies offer cutting-edge opportunities to a growing field
- The Population Modelling Working Group is active under the Interagency Modelling and Analysis Group (IMAG) umbrella
- Members meet annually at the IMAG meeting at the National Institutes of Health
- The working group maintains a web portal and a mailing list.

The project

- An attempt to illustratively map the field of population modelling
- Motivated by problems in medicine and biomedical sciences
- Our working definition of population modelling:

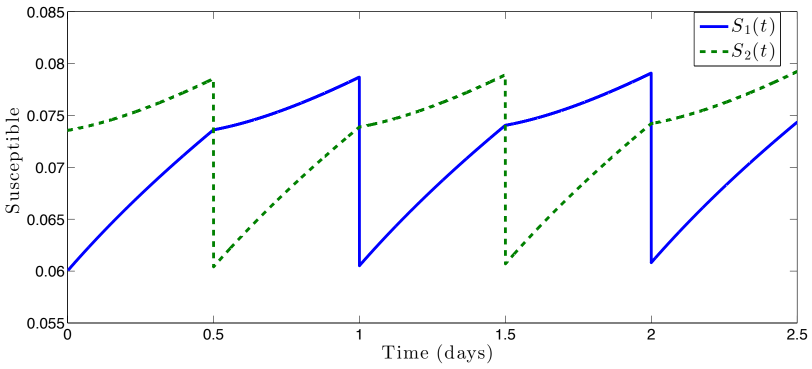
> *"Tackling real-life problems that are relevant at the population level using a range of mathematical tools"*

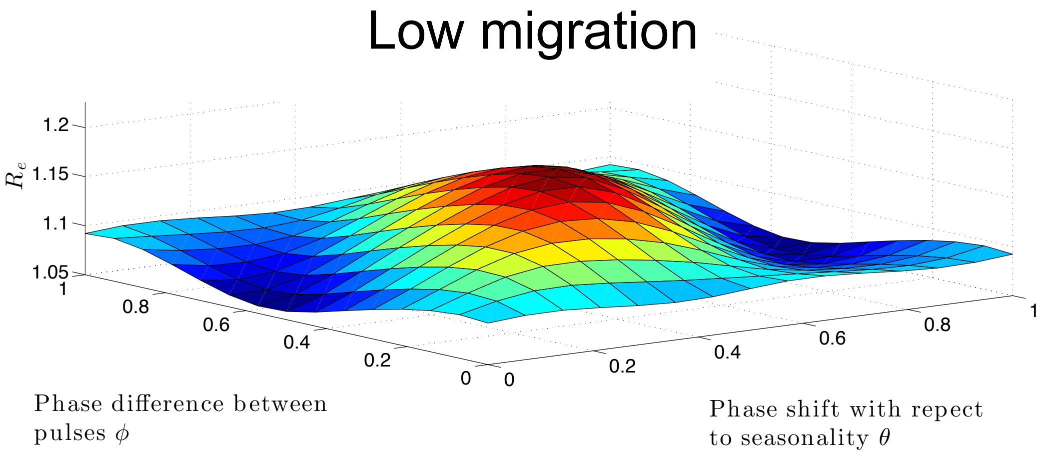
- However, this is imprecise, so we demonstrate by way of examples.

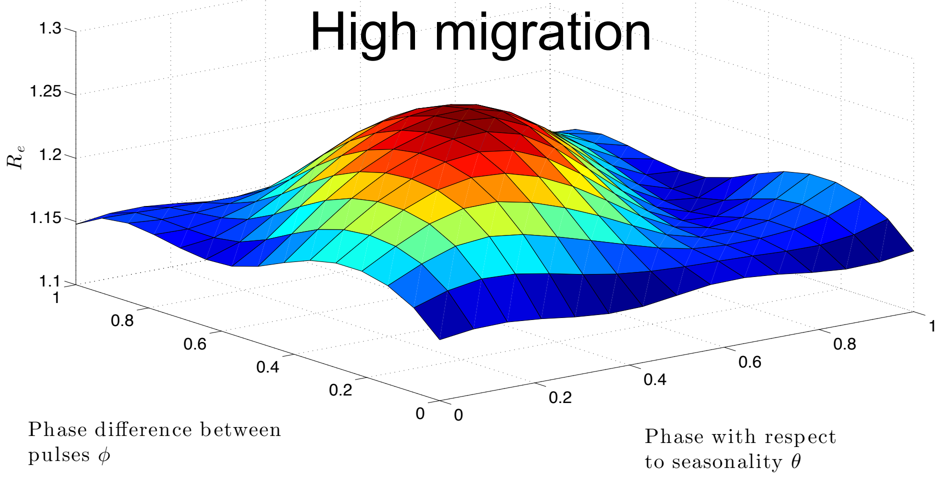
Robert Smith? (University of Ottawa, Canada)

Polio eradication with synchronised impulses

$$
\begin{aligned}
\frac{dS_i}{dt} &= (1-p_i)b_i - \mu_i S_i - S_i \sum_j \beta_{ij}(t) I_j - S_i \sum_j \epsilon_{ij}(t) G_j + \sum_j m_{ij} S_j & t \neq t_{i,n}\\
\frac{dI_i}{dt} &= S_i \sum_j \beta_{ij}(t) I_j + S_i \sum_j \epsilon_{ij}(t) G_j - (\mu_i + \gamma_i) I_i + \sum_j k_{ij} I_j & t \neq t_{i,n}\\
\frac{dG_i}{dt} &= \xi_i(t) I_i - \nu_i(t) G_i & t \neq t_{i,n}\\
\frac{dR_i}{dt} &= p_i b_i + \gamma_i I_i - \mu_i R_i + \sum_j l_{ij} R_j & t \neq t_{i,n}\\
S_i\left(t_{i,n}^{+}\right) &= \left(1-\psi_{i,n}\right) S_i\left(t_{i,n}^{-}\right) & t = t_{i,n}\\
R_i(t_{i,n}^{+}) &= \psi_{i,n} S_i(t_{i,n}^{-}) + R_i(t_{i,n}^{-}) & t = t_{i,n}.
\end{aligned}
$$

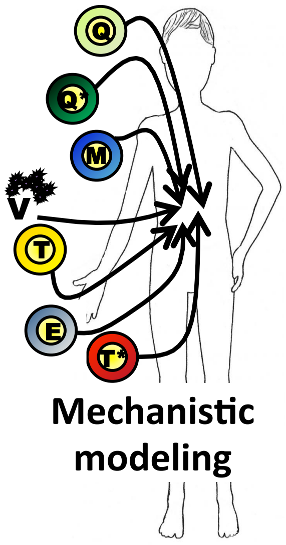




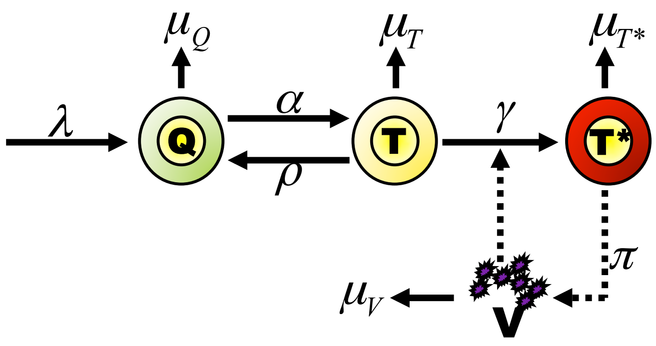


Melanie Prague (Harvard, USA)

Mechanistic modelling of cell population dynamics: targeting HIV drug doses



Mechanistic modeling



Mathematical model (ODE)

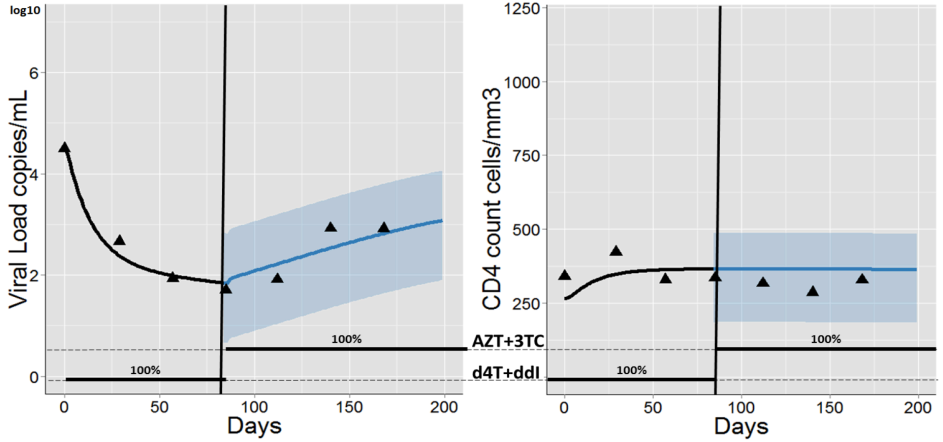
$$\left\{\begin{aligned} dQ/dt &= \lambda^i - \mu_Q Q - \alpha Q + \rho T \\ dT/dt &= \alpha Q - \rho T - \mu_T T - \gamma^i(t,TRT)VT \\ dT^*/dt &= \gamma(t,TRT)VT - \mu^i_{T*}T^* \\ dV/dt &= \pi T^* - \mu_V V \end{aligned}\right.$$

Statistical model (NLME)

$$\tilde{\gamma}^i(t,TRT) = \tilde{\gamma}_0 + \beta TRT^i(t) + u^i_\gamma$$
$$u^i_\gamma \sim N(0,\sigma_\gamma)$$

- **Good predictive abilities**

Predictions of biomarkers with 95% predictivity intervals



- **Base reproduction Number (R_0)** characterizes equilibrium leading to infection control and, thus **optimal individual dose (d^i_{opt})**.

$$P(R_0^i(d^i_{opt},\lambda^i,\alpha^i,\ldots,\gamma^i)<1) = 90\%$$

Matthias Chung (Virginia Tech, USA)

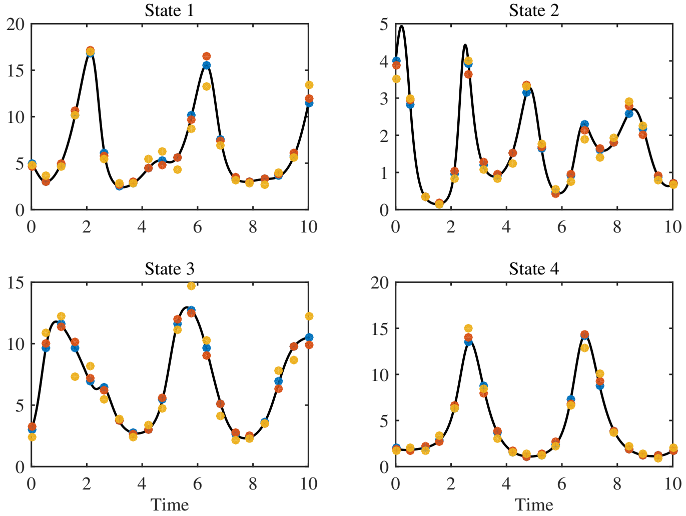
Parameter Estimation for Population Dynamics

Parameter estimation for *generalized Lotka-Volterra* system

$$\min_{\mathbf{r},\mathbf{A}} \|\mathbf{m}(\mathbf{y}) - \mathbf{d}\| \quad \text{subject to} \quad \mathbf{y}' = \operatorname{diag}(\mathbf{y})(\mathbf{r} + \mathbf{A}\mathbf{y})$$

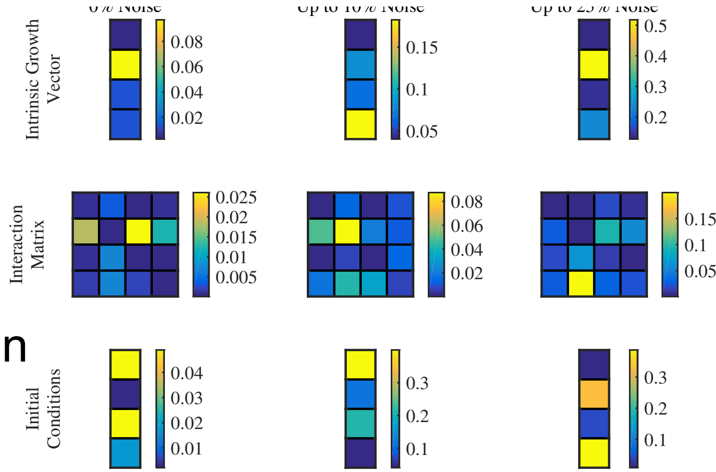
$\mathbf{d}$	observation of species
$\mathbf{y}$	abundance of species
$\mathbf{m}$	projection operator

	distance measure
$\mathbf{r}$	intrinsic growth
$\mathbf{A}$	interaction matrix



Challenges:

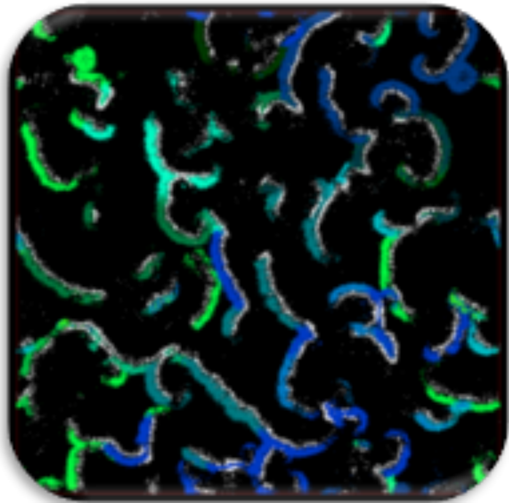
- Complex population dynamics need to be captured leading to investigation of chaotic dynamical system
- Non uniqueness and ill-posedness of parameter estimation problem
- Numerical optimization difficult through non-existence of solution of the dynamical systems



Robin Gras (University of Windsor, Canada)

EcoSim: An artificial world for exploring ecological questions

- Very large populations of “intelligent”, evolving agents
- Three trophic levels: grass, prey, predators
- Genome coding for behaviour and physical properties
- Thousands of generations in a few weeks
  - Speciation and species extinction
  - Predator effects on prey behaviour and evolution
  - Sexual/asexual reproduction
  - Invasive species
  - Emergence of communication
  - Emergence of altruism
  - Ecotoxicology.



Valery Forbes (University of Minnesota, USA)

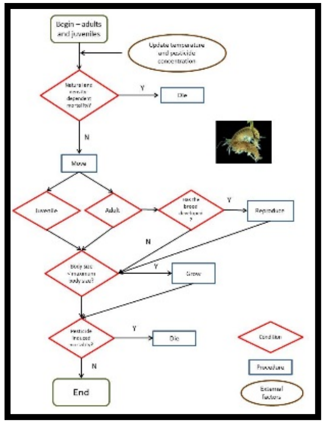
Linking effects of toxic chemicals from the organismal to population level

- Ecological protection goals usually involve populations, not individuals
- We measure effects of toxic chemicals on individual survival, growth and reproduction
- These have variable consequences for population dynamics
- Population models can extrapolate what we need to measure and what we need to protect.

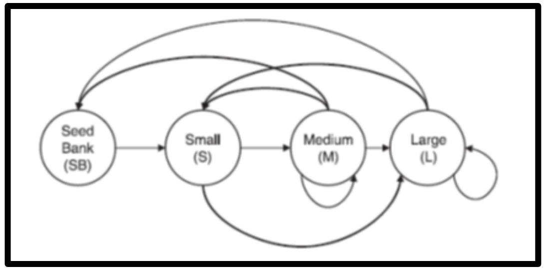
$$\frac{dA}{dt} = \mu NA - \frac{a_{AX}AX}{1 + a_{AX}h_{AX}A + a_{DX}h_{DX}D} - d_A A - e_A A$$

$$\frac{dN}{dt} = I_N + \frac{(1-\delta_{AX})a_{AX}\gamma_{AX}AX}{1 + a_{AX}h_{AX}A + a_{DX}h_{DX}D} + \frac{(1-\delta_{DX})\gamma_{DX}a_{DX}DX}{1 + a_{AX}h_{AX}A + a_{DX}h_{DX}D} + mD - \mu NA - e_N N$$

Scalar Model



IBM

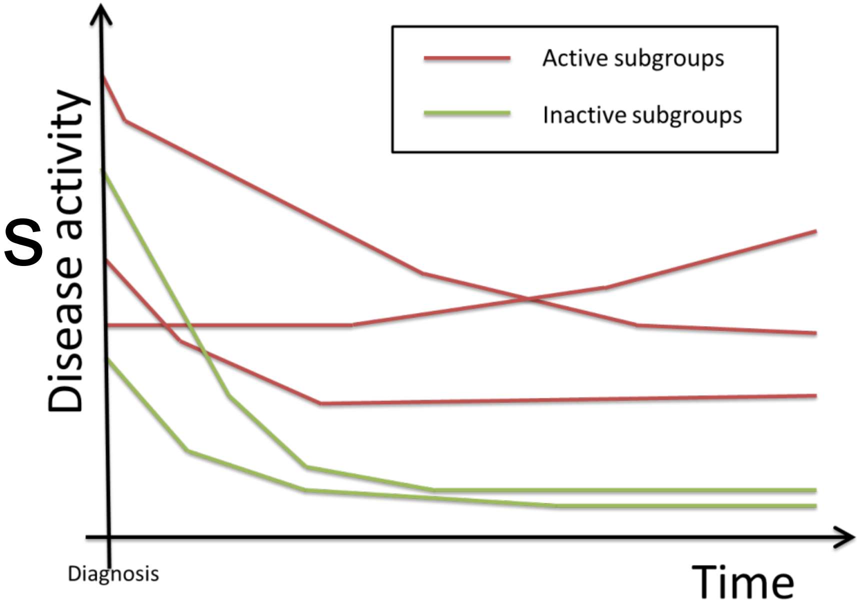


Matrix Model

Sixten Borg (Lund University, Sweden)

Heterogeneity in disease activity and cost-effectiveness analysis

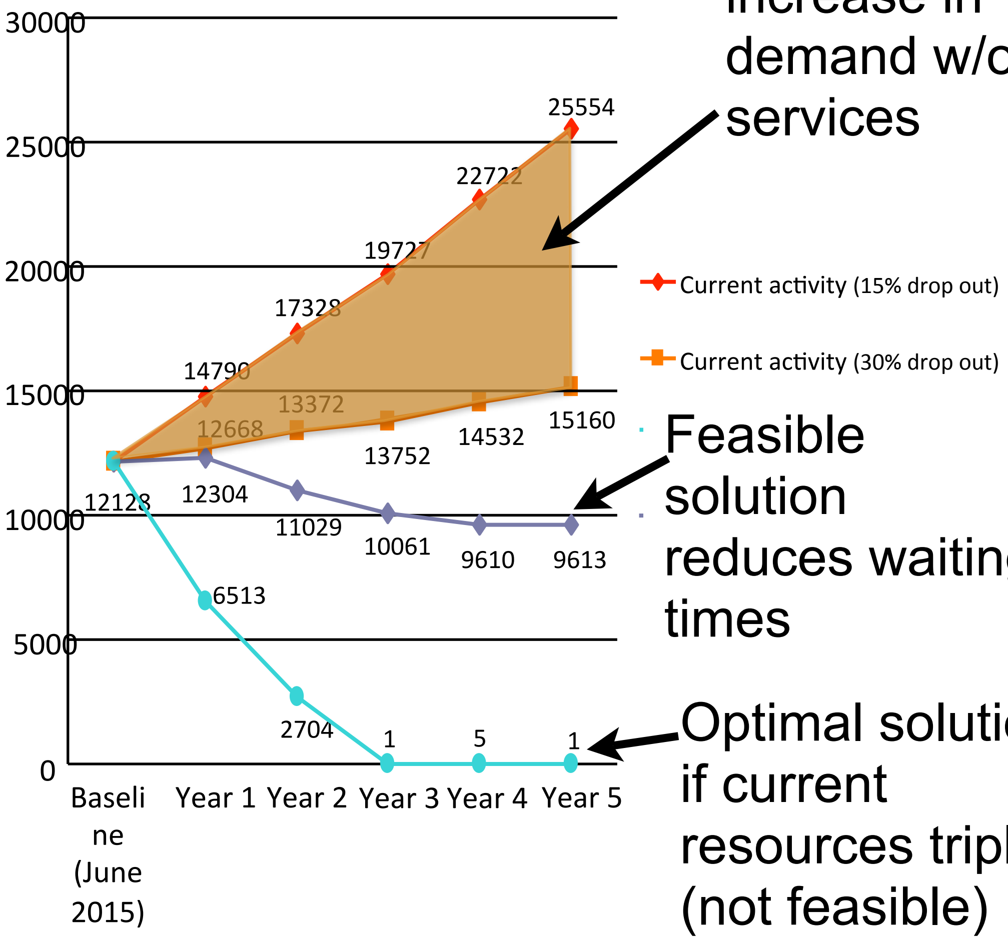
- An intervention's cost-effectiveness can vary by subgroup due to patient heterogeneity
- We use finite mixtures of disease activity models to identify relevant subgroups
- Characteristics of subgroups and their cost-effectiveness inform decisions on resource allocation.



Tracy Comans (Griffith University, Australia)

Estimating demand for orthopaedic specialist services in Australia

- Identify the gap between demand and service capacity
- Identify patients who would be suitable for physiotherapy-led management
- Develop recommendations to address current and future gaps in services.



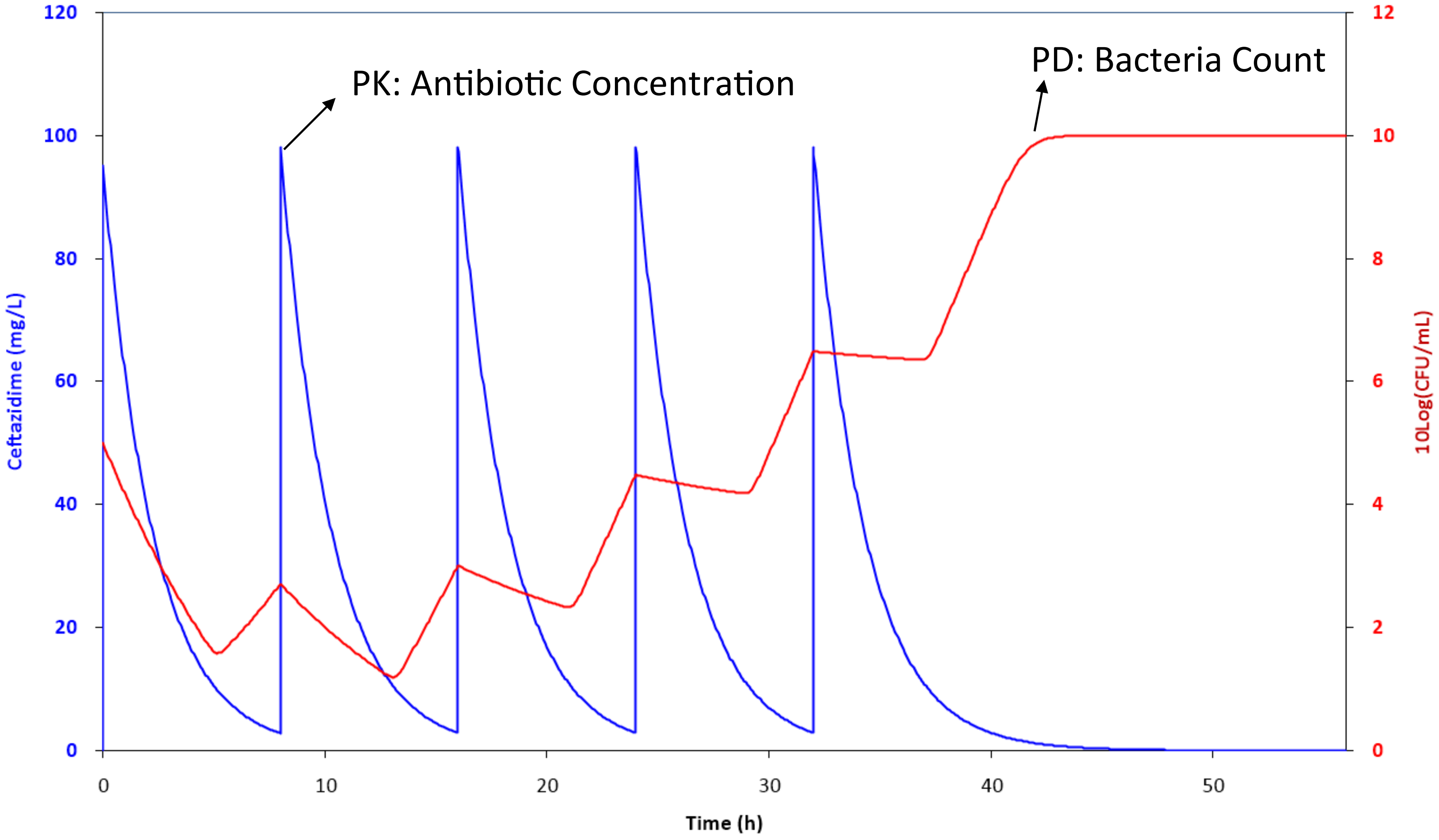
Projected increase in demand w/o services

Feasible solution reduces waiting times

Optimal solution if current resources triple (not feasible)

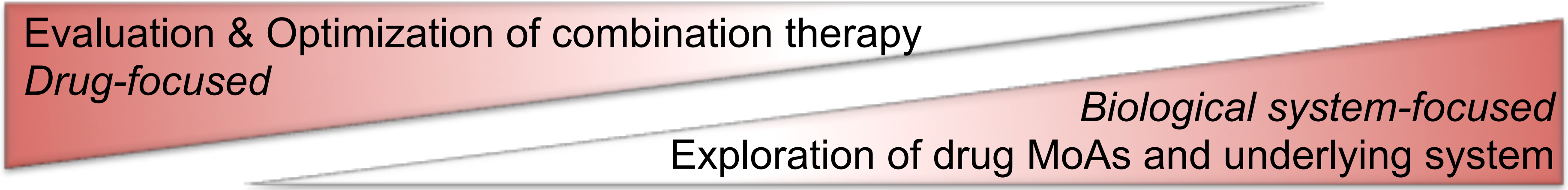
Neiko Punt (Medimatics, The Netherlands)

Visual PKPD Modelling Using EDSIM++



William J. Jusko (University of Buffalo, USA)

Chemotherapy Systems Modelling



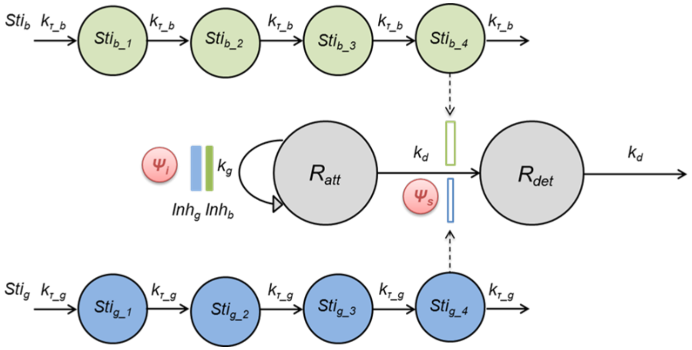
Evaluation & Optimization of combination therapy

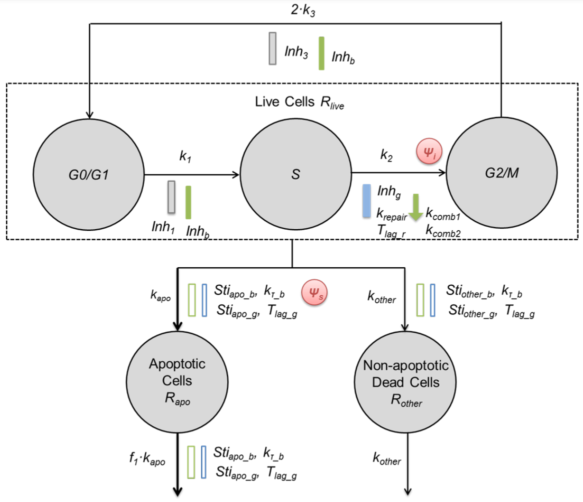
Drug-focused

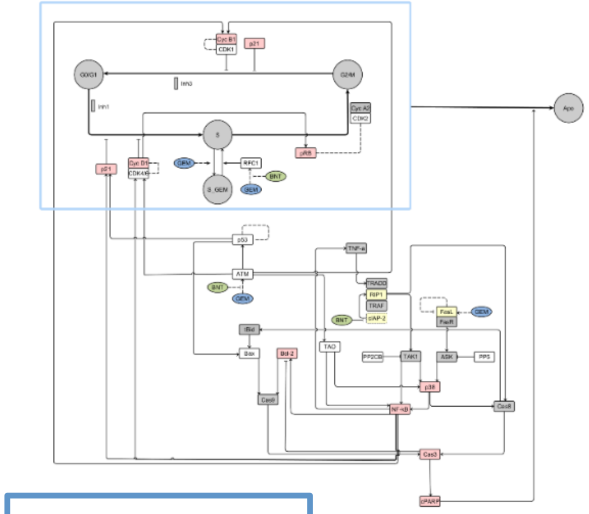
Biological system-focused

Exploration of drug MoAs and underlying system

Basic PD Model → Mechanism-Based PD Model → Network Model







Cell culture studies

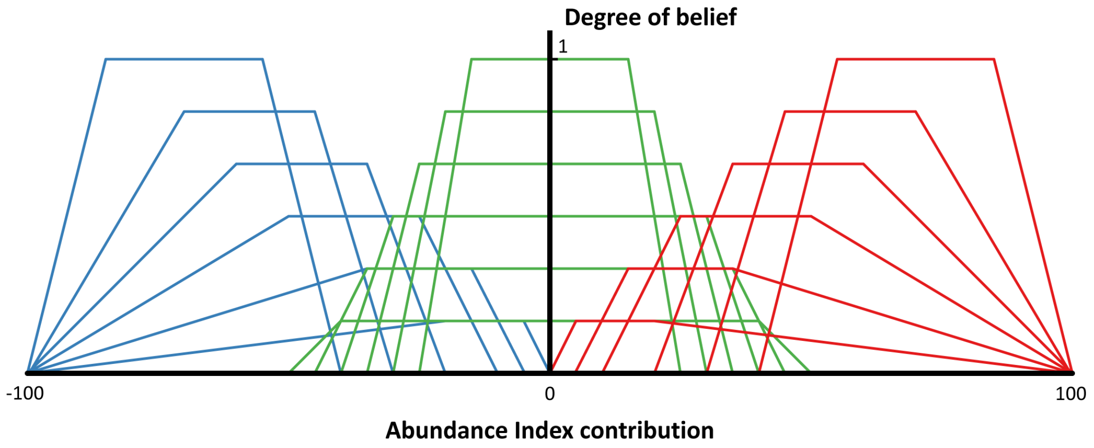
Assessing cell-cycle drug effects

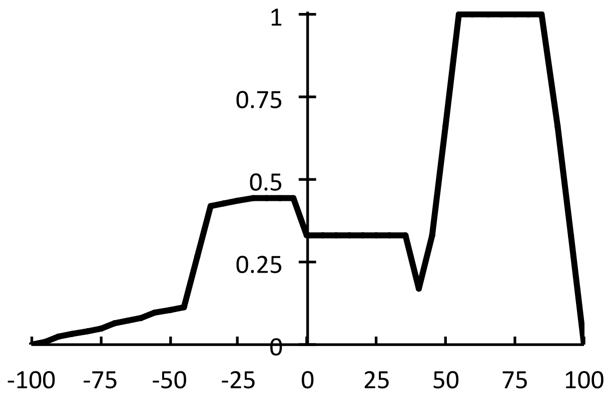
Genomic and proteomic studies

New targets or combinations for evaluation

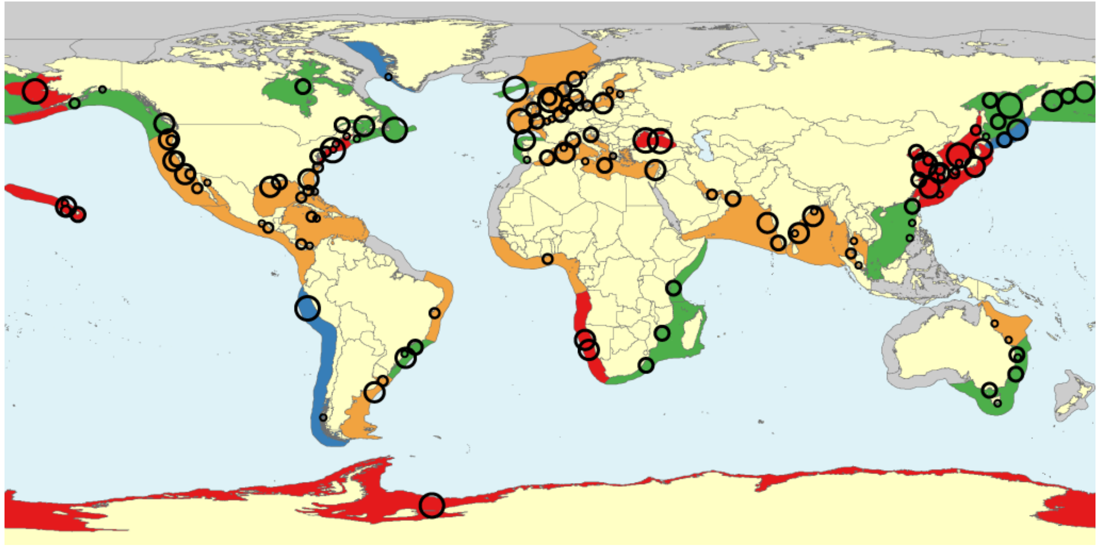
Lucas Brotz (University of British Columbia, Canada)

Examining population trends using fuzzy logic





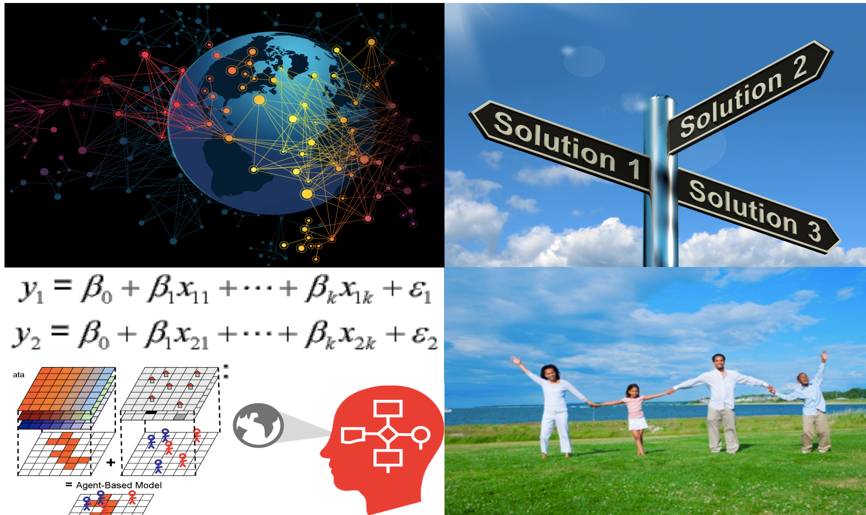
- Fuzzy logic represents variables according to a degree of membership
- Applied to global jellyfish populations
- Suggests populations are increasing in coastal ecosystems



Ayaz Hyder (Ohio State University, USA)

Systems Science in Epidemiology

- Systems science methods integrate data, develop explanatory models and evaluate solutions for better outcomes
- Eg agent-based models of influenza spread
- Microsimulation models for cost-effectiveness of cancer surveillance
- Satellite-based predictions for air pollution exposure and risk of birth outcomes.



Discussion

- Through heterogeneous examples, we illustrate how the field has been conceptualised and evolved
- However, we are still not at the limit of the field’s potential
- We see a range of applications and tools
- Yet there is also unity, with a focus on utilising computation and theoretical methods as tools for tackling a multitide of problems
- We posit an alternate, two-dimensional view:

Contributor	Disease spread	Resource allocation	Drug effects	Risk assessment	Ecosystem management	Testing theory	Epidemiology/ Public health	Methods
Robert Smith?	x		x				x	Impulsive DEs, Latin hypercube sampling
Bruce Y. Lee	x						x	ABMs
Aristides Moustakas	x							ABMs
Andreas Zeigler				x				Random forests, support-vector machines
Mélanie Prague	x		x				x	ODEs, control theory
Romualdo Santos		x			x			Difference equations
Matthias Chung						x		Point-estimator methods for ODEs
Robin Gras					x	x		ABMs, fuzzy maps
Valery Forbes				x		x		Matrix models, ABMs
Sixten Borg		x	x				x	Finite mixtures, cost-effectiveness analysis
Tracy Comans		x					x	Discrete event simulation, cost-effectiveness analysis
Yifei Ma	x	x					x	Network models, diffusion dynamics
Neiko Punt			x					PKPD modelling, Bayesian estimates
William Jusko			x			x		PKPD modelling, ODEs
Lucas Brotz					x	x		Fuzzy logic analysis
Ayaz Hyder		x		x		x	x	ABMs, microsimulation models

Future challenges

- As data become increasingly available, questions of security become more prominent
- Big data are an excellent resource but can result in big privacy violations
  - eg the Ashley Madison hack, Wikileaks, Edward Snowden's NSA data release
- Gathering large amounts of data in one place opens that data up to susceptibility on an unprecedented scale
- This can be a force for good or a massive privacy violation.

Ethical implications

- As scientists, it behooves us to consider the ethical and moral implications of our work
- A growing challenge is the melding of the physical sciences with the social sciences
- If human behaviour is to be understood, modelling must draw upon fields that have expertise in the qualitative understanding of social, cultural and behavioural norms
- This cross-disciplinary understanding is necessary to improve our quantitative models.

Conclusion

- Any attempt at a comprehensive definition is of course futile
- However, through the examples given here and in a similar paper last year, we see snapshots of the field in time
- The mailing list is open to new members
- We encourage discussion and future contributions

https://simtk.org/mailman/listinfo/popmodwkgrpimag-news

- In this way, we may eventually have a sense of the shadow of the field, if not its shape
- The project continues...